I. The Office Action

The November 29, 2007 non-final office Action (the "Office Action") in this application:

1. denied priority of claims 1-2, 4-5, 29, 47, and 63 under 35 U.S.C. section 119 to parent application 08/173,996.

2. rejected claims 1-2, 4-5, 29, 47 and 63 under 35 U.S.C. section 112, first paragraph for lack of enablement.

3. rejected claims 1-2, 4-5, 29, 47 and 63 under 35 U.S.C. section 103(a) as being unpatentable over Balkan (1991) ) or Han (2001) in view of Kohl (2000) and Tse (1982) and Aoki (U.S. patent 6,113,915, filed in 1999).

4. rejected claims 1-2, 4-5, 29, 47 and 63 under 35 U.S.C. section 103(a) as being unpatentable over Balkan (1991) ) or Han (2001) in view of Kohl (2000) and Aoki (U.S. patent 6,113,915, filed in 1999) and Aoki (patent publication 2001 018415).

Applicants respond to the Office Action as follows.

II. Denial of Domestic Priority under 35 U.S.C. Section 120

The Office Action denied priority of claims 1-2, 4-5, 29, 47 and 63 under 35 U.S.C. section 119 to parent application 08/173,996, filed December 28, 1993. It is believed that the Office Action intended to deny priority under 35 U.S.C. section 120, because only domestic priority (section 120) not any foreign priority (section 119) has been claimed by applicants.

Priority to parent application serial number 09/176,996, filed December 28, 1993 ("the '996" application) was denied because as viewed by the Office Action the specification of the '996 application does not provide section 112, first paragraph "how to use" enablement to claims 1-2, 4-5, 29, 47 and 63.

Applicants present herein additional evidence and argue that the pending claims are enabled by the '996 application and that therefore the denial of priority to the '996 application should be withdrawn and priority for the claims granted to the '996 application filed December 28, 1993.

III. Rejection Under 35 U.S.C. Section 112, First Paragraph

The Office Action denied priority of the claims to the December 28, 1993 filing date of the parent '996 application because in the view of the Office Action the claims are not "how to use" enabled, as required by 35 U.S.C., section 112, first paragraph. Respectfully, the rejection is in error and should be withdrawn.

To summarize the Office Action, the enablement rejection was made on the basis that: (1) Schantz et al, *Properties and use of botulinum toxin and other microbial neurotoxins in medicine*, Microbiol Rev 1992 Mar; 56(1): 80-89 ("Schantz 1992") states that the neurotoxic component of a botulinum toxin ("the neurotoxic component") is unlikely to be used in a clinical setting; (2) applicants relied upon the statements in Schantz 1992 to show a teaching away from the claimed invention, and; (3) in the view of the Office Action the parent specification (i.e. the '996 application) does not enable the claimed invention because in light of the teaching away by Schantz 1992 undue experimentation would be required to practise the claimed invention.

Thus, the Office Action states:

1. "...the rejection was based on the fact that the specification did not provide ample guidance on 'how to use' the neurotoxic component in a clinical setting. (page 7 of the Office Action)

2. "Further, Applicants did not provide any guidance to one of ordinary skill in the art how one could avoid the problems associated with purified botulinum toxin component" (i.e. as set forth in Schantz 1992) (page 9 of the Office Action).

3. "As indicated by Schantz et al. the teachings of complexed toxin could not be utilized [for] purified botulinum toxin since the purified portion is so labile that it would not be used in clinical settings." (page 9 of the Office Action).

Additionally, near the bottom of page 9 and continuing to page 10 of the Office Action it is stated that a reference between the date of Schantz 1992 and the December 1993 filing date of the '996 application could assist to rebut the prejudice (i.e. the teaching away) created by Schantz 1992 regarding the claimed clinical use of the neurotoxic component.

Respectfully, the bases raised by the Office Action for the lack of enablement rejection under section 112, first paragraph and hence for denial of priority to the '996 application is incorrect and the rejection should be withdrawn because of the evidence set forth in the Brin Declaration and in the newly presented Smith declaration. Applicants ask the examiner to reconsider the Brin declaration. The Smith declaration provides evidence that Schantz 1992 was wrong when he said that the neurotoxic component is unlikely to be used clinically. The Smith declaration also provides evidence showing that no special formulation or process was required to make a clinically useful neurotoxic component formulation. Finally, the Smith declaration states that the '996 application provides ample guidance for clinical use of the neurotoxic component.

1. The Brin Declaration

The March 28, 2007 Brin declaration (submitted with the response applicants filed April 12, 2007) states that the person of ordinary skill "would have been able with little or no difficulty to obtain the neurotoxic component of a botulinum toxin so as to be able to use the neurotoxic component to treat a patient with one or more of the Disorders" (i.e. the claimed strabismus) (paragraph 17 of the Brin declaration). Additionally, paragraph 19 of the Brin declaration reiterates that "...the Physician would have been able to easily proceed to treat a patent suffering from a Disorder with the neurotoxic component of a botulinum toxin based on the disclosure and guidance provided by the '996 application". Multiple factual bases for this expert opinion are provided in paragraph 18 of the Brin declaration.

The Office Action found the Brin declaration unpersuasive to rebut the lack of enablement rejection stating "...the Declaration does not provide any evidence to counter the contentions raised by Schantz et al." (page 6 of the Office Action).

Respectfully, the entire Brin declaration is "evidence" which should be considered by the examiner, including paragraph 18(c) of the Brin declaration which states "the '996 application gives particulars as to how a physician can administer the neurotoxic component...". Additionally, as can be understood from the Smith declaration, no evidence is required to counter the contentions raised by Schantz 1992 because Shantz 1992 was wrong and is therefore irrelevant with regard to and can have no bearing upon whether of not the specification of the '996 application is enabling.

Hence the examiner is asked to reconsider the Brin declaration which is the expert opinion by a noted clinician with many years therapeutic use of botulinum toxin, noting the factual bases for the opinion by Dr. Brin that the person of ordinary skill "would have been able with little or no difficulty to obtain the neurotoxic component of a botulinum toxin so as to be able to use the neurotoxic component to treat a patient with one or more of the Disorders" (i.e. the claimed strabismus), and based thereupon withdraw the lack of enablement rejection.

2. The Smith Declaration

Attached is the November 20, 2007 declaration of Dr. Leonard Smith presented as providing evidence to rebut the section 112, first paragraph enablement rejection. Dr. Smith has "extensive experience characterizing and formulating the neurotoxic component of a botulinum toxin" (Smith dec ¶8) and is "an expert in the properties of the neurotoxic component" (Smith dec ¶11).

The Smith declaration provides two main types of evidence. Firstly in paragraphs 13-16 of the Smith declaration there is evidence that the statement in Schantz 1992 that the neurotoxic component is unlikely to be used in a clinical

setting is "clearly wrong". Secondly in paragraphs 17-18 of the Smith declaration there is evidence that the '996 application "clearly and explicitly discloses" how to use the neurotoxic component in a clinical setting.

A. Schantz was Wrong

The declarant Dr. Smith carefully read Schantz 1992 (Smith dec ¶11) and understands that Schantz 1992 makes statements regarding lack of clinical utility of the neurotoxic component (Smith dec ¶14). The Smith declaration presents in paragraph 15 four separate factual bases upon any one of which it can be concluded that the statements in Schantz 1992 that the neurotoxic component is unlikely to be used in a clinical setting are clearly wrong:

(1) the statements in Schantz 1992 are mere conjecture and unsupported opinion statements. Smith dec ¶15(a). This was determined by the declarant from a careful review of Schantz 1992. Smith dec ¶15(a).

(2) the statements in Schantz 1992 have been challenged in the literature. Smith dec ¶15(b).

(3) after the March 1992 publication date of Schantz 1992 but before the December 1993 filing date of the '996 application it was known that a storage stable formulation of the neurotoxic component could be administered to varous mammal species with physiological effect. Smith dec ¶15(c). Importantly, this third basis upon which it can be concluded that the statements in Schantz 1992 that the neurotoxic component is unlikely to be used in a clinical setting are clearly wrong, provides the evidence requested on pages 9-10 of the Office Action:

"...evidence, between the date of Schantz et al., and the filing date of the present application, to rebut how at the time of filing the present application, one of ordinary skill would consider using only the purified botulinum toxin component of the botulinum toxin in clinical settings, given that Schantz et al. clearly stated that purified botulinum toxin is so labile that it would not be used in clinical settings."

(4) concurrenty with the December 1993 filing date of the '996 application it was known that the a stable, active formulation of neurotoxic component could be made in the same way and using the same excipients used to make a stable, active formulation of a botulnium toxin complex. Smith dec ¶15(d).

This fourth basis upon which it can be concluded that the statements in Schantz 1992 that the neurotoxic component is unlikely to be used in a clinical setting are clearly wrong was determined from work being carried out concurrent with the filing of the '996 application, as evidenced by the detailed, extensive multi-month work presented in the Goodnough Ph.D thesis published March 1994.

The attached redacted letter dated September 17, 2007 from the Wisconsin Alumni Research Foundation, signed by Laura M. Heisler Ph.D, Intellectual Property Manager, confirms the March 10, 1994 date of availability of the Goodnough Ph.D thesis as a printed publication. It is well known that a single copy of a cataloged thesis in one university library can constitute a printed publication for art purposes. *In re Hall*, 781 F2d 897, 228 USPQ 453 (Fed. Cir. 1986).

It is important not to under estimate the importance of the disclosure in the Goodnough Ph.D thesis. When one remembers that Schantz 1992 states on page 89 that the neurotoxin component is unlikely to be used in a clinical setting because in Schantz's opinion the neurotoxic component is "inactivated on dilution, formulation and drying", and then notes that in direct contradiction thereto the Goodnough Ph.D thesis based on extensive experimental work states

that when the neurotoxic component and the botulinum toxin complex were both seperately lyophilized and dried with albumin "recoveries on drying [the neurotoxic component] were similar to those obtained with the complexes" (see Smith dec ¶15(d)G, and Goodnough thesis page 137) and that "Recovery of activity following lyophilization of purified type A and B neurotoxin does not seem to be dependant on the presence of the non-toxic binding proteins of the complex as a high percentage of toxin activity was recovered using the same formulation as that used for the type A and B toxin complexes." (Smith dec ¶15(d)H and Goodnough thesis page 142, emphasis added), then it could not be clearer that Schantz 1992 was wrong, that is that a stable formulation of the neurotoxic component can be prepared using the same formulation made by the same process used to make a stable botulinum toxin complex formulation.

Each of these four bases show that while the statements in Schantz 1992 do in fact teach away from clinical use of the neurotoxic component, these statements in Schantz 1992 are wrong.

Since Schantz 1992 was wrong Schantz 1992 is therefore irrelevant with regard to and can have no bearing upon whether of not the specification of the '996 application is enabling.

B. The Specification Enables the Claims

As set forth above, the Smith declaration provides evidence that Schantz 1992 was wrong where it says that the neurotoxic component lacks clinical utility. This evidence is presented in part by showing that a clinically useful neurotoxic component formulation can be made in the same way that a clinically useful botulinum toxin complex formulation can be made. The Smith declaration then continues in paragraphs 17-18 with evidence that the '996 application "clearly and explicitly" discloses how the person of ordinary skill can use the neurotoxic component in a clinical setting. Smith dec ¶17.

Thus, the Smith declaration notes that the '996 application discloses on page 3 that the neurotoxic component is "useful in the present invention" and that the '996 application is thereby "directly and immediately stating that the neurotoxic component can be used to treat the various disorders set forth in the '996 application", which disorders include the claimed strabismus. Further, the Smith declaration notes that the '996 application discloses "how to formulate, stabilize and reconstitute the neurotoxic component, using the same process used to formulate, stabilize and reconstitute the botulinum toxin complex" (Smith dec ¶17(b)), which as explained in the Goodnough Ph.D thesis will result in a neurotoxic component formulation at least as potent as a botulinum toxin formulation made the same way, by the same process, using the same reagents and excipients, as used to make a clinically useful neurotoxic component formulation.

Thus, since as evidenced by the Smith declaration no special process or formulation is required to obtain a clinically useful neurotoxic component, despite statements by Schantz 1992 to the contrary, therefore the disclosure in the '996 application is sufficient to enable a person of ordinary skill to practice the claimed invention without undue experimentation. Hence, the Smith declaration rebuts and overcomes the lack of enablement rejection in the Office Action.

Finally, applicants would like to address the statements made in several places on pages 7-9 of the Office Action regarding applicant's use of Schantz 1992 as a teaching away reference to show non-obviousness of the claimed invention. Schantz 1992 says what it says and therefore when Schantz 1992 states that the neurotoxic component is unlikely to be used clinically Schantz 1992 teaches away from and renders unobvious the claimed invention. Applicants have presented evidence that Schantz 1992 was wrong and that therefore a person of ordinary skill could in fact make and clinically use the neurotoxic component, as claimed, using the disclosure and guidance provided by the '996 application. Hence, Schantz does still render the claims not obvious

(i.e. Schantz says what it says) but does not render the specification non-enabling (i.e. Schantz was wrong and the specification in enabling). As stated in *Singh v. Brake*, 65 USPQ 2d, 1641 at 1650 (Fed. Cir. 2003) "Although the questions (1) whether or not a reference 'teaches away' from a claimed invention and (2) whether or not a claimed invention provides 'unexpected results' are relevant in determining whether not a claimed invention would have been obvious, they are not the primary questions bearing on enablement".

IV. The Claims Meet the Legal Standard for Enablement

The test for enablement in the present circumstances is whether one skilled in the art at the time the '996 application was filed could make and use the claimed invention from the disclosures in the specification coupled with the information known in the art without undue experimentation. In re Vaeck, 947 F.2d 488 (Fed. Cir. 1991).

Factual considerations that can be weighed when determining whether "undue" experimentation would be required include: (1) the breadth of the claims, (2) the nature of the invention, (3) the state of the prior art, (4) the relative skill of those in the art, (5) the predictability or unpredictability of the art, (6) the amount of direction or guidance provided, (7) the presence or absence of working examples, and (8) the quantity of experimentation necessary. See *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Any part of the specification can support an enabling disclosure, including a background section that discusses or even disparages the subject matter disclosed therein. *Callicrate v. Wadsworth Mfg., Inc.*, 427 F.3d 1361, 1374 (Fed. Cir. 2005). All the evidence must be considered, and any conclusion of nonenablement must be based on the evidence as a whole. MPEP § 2164.01(a).

Applicants respectfully submit that an analysis of all the relevant evidence reveals that applicant's '996 application as filed is such that one of ordinary skill in the art would have been able to make and use the claimed invention without undue experimentation.

The *In re Wands* considerations set forth above can be reviewed to assist an evaluation of enablement of the claimed subject matter:

1. *Nature of the Invention*

The claimed invention is a method for treating strabismus using the neurotoxic component of a botulinum toxin. The '996 application provides more than sufficient guidance to one of ordinary skill regarding the claimed invention. For example, the '996 application provides guidance at page 4, lines 9-12, regarding known techniques to purify botulinum toxins. The '996 application provides guidance at page 4, lines 14-19, regarding botulinum toxins that are available from commercial sources, and provides examples of such sources. The '996 application also provides guidance at page 7, line 11 to page 8, line 10 regarding techniques for administering purified neurotoxic component.

2. *State of the Prior Art*

The state of the art, as set forth above was that it was well known how to obtain the neurotoxic component of a botulinum toxin without undue experimentation. Thus, for example, one of ordinary skill would have known that the neurotoxic component, either single chain or dichain, was obtained by fermentation of Clostridium botulinum followed by chromatographic separation techniques. See Brin Declaration ¶18(a). One of ordinary skill would have known that neurotoxic component was available for purchase from commercial suppliers. See Brin Declaration ¶18(b). One of ordinary skill would have known the techniques for administration of the neurotoxic component, e.g., by intramuscular administration. See the Brin Declaration at ¶18(c).

Schantz 1992 cited on page 4 of the Office Action states on page 89 that "it is unlikely that [the neurotoxic component] will be used in a clinical setting." However, Schantz 1992 do not characterize the state of the art as bleak. Rather, Schantz 1992 indicates a long felt need for other botulinum toxin types for clinical use ("...it is likely that types other than type A will be used clinically...") (page 86, left hand side column). Additionally, Schantz 1992 was wrong. See the Smith Declaration at ¶15.

3. *Relative Skill of those in the Art*

The relative skill in those in the art was high, as the person of ordinary skill in the art can be characterized as a physician with knowledge of or experience using botulinum toxin. See the Brin Declaration ¶15 and the Smith Declaration at ¶16.

4. *Predictability of the Art*

It was well known to the prior art that the neurotoxic component is the biologically active component of a botulinum toxin. See Brin declaration ¶16. Therefore the predictability of therapeutic efficacy upon use of the neurotoxic component must be considered to be high or very predictable.

5. *Breath of the Claims*

The breadth of the claims is narrow because the claims are limited to treatment of the single, specific disorder strabismus using a single specific active agent, the neurotoxic component of a botulinum toxin.

6 and 7. *Guidance Provided and Presence of Working Examples*

The '996 application discloses at page 4, lines 9-12 that a botulinum toxin can be purified (i.e. so as to obtain the neurotoxic component) and then stabilized and preserved (see eg page 7, lines 21-28 of the '996 application). Additionally, the claimed invention is directed to a method in which the neurotoxic component administered has been obtained by the purification of a botulinum toxin provided

by fermentation of a Clostridium botulinum. And as explained in paragraph 18 of the Brin declaration the '996 application provides guidance to one of ordinary skill, in light of the teachings of the prior art, as to how to obtain the neurotoxic component used in the claimed method without undue experimentation. Additionally, as explained in paragraph 17 of the Smith declaration the '996 application "clearly and explicitly" tells the person of ordinary skill how to use the neurotoxic component in a clinical setting.

Additionally, the '996 application discloses the different components of a botulinum toxin and clearly indicates that one can use the neurotoxic component; see eg page 3, lines 23-25 that both forms (single and dichain) of the neurotoxic component "are useful in the method of the present invention".

Regarding examples, the '996 application explicitly states at page 3, lines 23-24 that the neurotoxic component of a botulinum toxin can be used in the methods of the invention. Hence, it cannot be clearer that the Examples of the invention on pages 10-20 of the '996 application all encompass use of the neurotoxic component.

8. *Quantity of Experimentation Necessary*

The weight of all the evidence is that one of ordinary skill in the art would have been able to make and use the claimed invention without any experimentation, based on the specification of the '996 application and knowledge of the prior art. See paragraphs 17 and 19 of the Brin declaration and paragraphs 17 and 18 of the Smith declaration.

For these reasons the lack of enablement rejection by the Office Action should be withdrawn.

V. Section 103(a) Rejection of Claims 1-2, 4-5, 29, 47 and 63

The Office Action rejected claims 1-2, 4-5, 29, 47 and 63 under 35 U.S.C. section 103(a) as being unpatentable over Balkan (1991) or Han (2001) in view of Kohl (2000) and Tse (1982) and Aoki (U.S. patent 6,113,915, filed in 1999). Respectfully, the rejection is in error and should be withdrawn for at least the following reasons:

1. Applicants have argued above and have presented evidence that the claims as amended are entitled to priority to the December 28, 1993 filing date of the '996 application. If applicants are granted the requested priority, the Han (published in 2001) and Kohl (2000) articles and the Aoki patent (filed in 1999) are not prior art with regard to the amended claims, thereby obviating and rendering moot a rejection of the claims over the combination of Balkan or Han in view of Kohl, Tse and Aoki '195.

2. A combination of the remaining references in the rejection, Balkan (1991) and Tse (1982), cannot create a *prima facie* case of obviousness of the amended claims obvious because Schantz, *Properties and use of botulinum toxin and other microbial neurotoxins in medicine*, Microbiol Rev 1992 Mar; 56(1): 80-89 (1992) discloses on page 89 that "it is unlikely that [the neurotoxic component] will be used in a clinical setting", thereby showing that the prior art teaches away from a combination of Tse with Balkan to thereby allegedly obtain the claimed invention.

It is well settled that a *prima facie* case of obviousness is only established if there is some suggestion or motivation to combine prior art references, and the teaching or suggestion to make the combination, together with the reasonable expectation of success, must both be found in the prior art as a whole, not based on Applicant's own disclosure. *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991). This requirement has been established to prevent the improper use of hindsight

combinations of prior art. To prevent such hindsight combinations, Federal Circuit case law "requires the examiner to show a motivation to combine the references that create the case of obviousness. In other words, the examiner must show reasons that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the matter claimed." *In re Rouffet*, 47 USPQ2d 1453, 1457-1458 (Fed. Cir. 1998). Applicants submits that no motivation to combine the Balkan and Tse references can exist. Thus, in light of the Schantz (1992) article, which is more nearly concurrent to the 1993 filing date of the '996 application as compared to the 1982 Tse article, there would have been no motivation to combine Balkan and Tse and certainly in view of Schantz (1992) no expectation of reasonable success if the combination was made.

For these reasons the rejection should be withdrawn

VI. Section 103(a) Rejection of Claims 1-2, 4-5, 29, 47 and 63

The Office Action rejected claims 1-2, 4-5, 29, 47 and 63 under 35 U.S.C. section 103(a) as being unpatentable over Balkan (1991) or Han (2001) in view of Kohl (2000) and Aoki (U.S. patent 6,113,915 filed in 1999) and Aoki (2001 018415). Respectfully, the rejection is in error and should be withdrawn for at least the following reason:

Applicants have argued above and have presented evidence that the claims as amended are entitled to priority to the December 28, 1993 filing date of the '996 application. If applicants are granted the requested priority, the Han (published in 2001) and Kohl (2000) articles as well as the Aoki '915 patent (filed in 1999) are not prior art with regard to the amended claims. Additionally, Aoki (2001 018415) as a divisional application having the same specification and same effective filing date as the '996 application, also cannot be prior art with regard to the amended claims. Hence, if priority to the December 28, 1993 filing date of the '996 application is granted the rejection is obviated and renders moot a rejection of the claims over the combination of over Balkan or Han (2001) in view of Kohl (2000) and Aoki (U.S. patent 6,113,915) and Aoki (2001 018415).

For these reasons the rejection should be withdrawn.

VII. Conclusion

All issues raised in the Office Action have been addressed. Examination and allowance of claims 1-2, 4-5, 29, 47 and 63 is requested.

Respectfully submitted,

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Dated: December 20, 2007

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